
(12) UK Patent Application (19) GB (11) 2 100 982 A

(21) Application No 8217983

(22) Date of filing 22 Jun 1982

(30) Priority data

(31) 48730

(32) 22 Jun 1981

(33) Italy (IT)

(43) Application published
12 Jan 1983

(51) INT CL³

A61K 31/52 31/195

C07D 473/08

(52) Domestic classification

A5B 170 180 20X 20Y

295 29Y 386 38Y 503 50Y

552 55Y 575 576 57Y H

C2C 1422 214 247 250

252 25Y 29X 29Y 30Y 351

352 386 635 761 764 802

80Y AA TL

U1S 1321 C2C

(56) Documents cited

GB 0624696

(58) Field of search

G1B

C2C

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(54) Antibronchospastic
water-soluble pharmaceutical
compositions

(57) Antibronchospastic water-soluble
compositions comprise the compounds
formed from theophylline and amino
acids, e.g. lysin or arginine.

GB 2 100 982 A

SPECIFICATION

Antibronchospastic water-soluble pharmaceutical compositions.

- 5 The present invention relates to antibronchospastic water-soluble theophylline salts with basic amino acids. More particularly the invention pertains to pharmaceutical compositions consisting of
- 10 theophylline water-soluble salts with lysine and arginine and to a process for preparing the same.
- It is well known from the prior art pertaining to bronchodilator pharmaceutical preparations that the theophylline (1,3-dimethylxanthine) is a natural substance characterised by significant antibronchospastic properties to be ascribed to the inhibition of the phosphodiesterase and to the increase of the intracellular AMPC.
- However, it is likewise known that the low water-solubility of theophylline does not allow the preparation of solutions having therapeutically significant concentrations so as to confine its use to preparations in the form of capsules, tablets and suppositories.
- 25 The procedures usually adopted at the present time to obtain a therapeutically acceptable water-solubility are based on the salification of the theophylline by means of organic bases such as ethylenediamine, choline, glucamine, and the products obtained thereby are well known and have long been used in therapeutic practice.

However it is to be pointed out that it has resulted from the clinical use, these products are not free from toxicity phenomena and in many cases do not

35 have an acceptable tolerance.

- Therefore it will be easily understood the increasing demand for a theophylline composition in which the necessary water-solubility is associated to a minor toxicity and an improved tolerance.
- 40 It appears that this problem may be satisfactory solved according to the present invention of preparing theophylline salts with basic amino acids, preferably lysine or arginine, which are pharmaceutically acceptable for producing pharmaceutical preparations having a theophyllinic activity.

The suggestion of utilising the lyophilised form is of great importance to allow the use of the composition in an aqueous solution, assuring an improved stability of the active constituent.

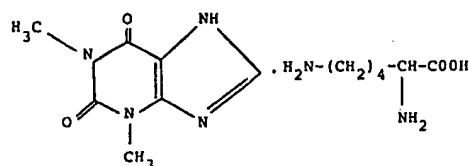
- Accordingly it is the main object of this invention to provide an antibronchospastic, water-soluble composition consisting of theophylline salts with a basic amino acid. In the preferred embodiment, as aforesaid, lysine or arginine is used as the basic amino acid.

The present invention will be now described in the following Examples with particular reference to some preferred embodiments.

Example 1.

60 Lysine Theophyllinate

Empirical formula : $C_{13}H_{22}N_6O_4$ Structural formula:



Molecular weight : 326.36

N contents : 25.76%

Composition : Theophylline 55.21%, Lysine

65 44.79%

Preparation process.

- 180.17 g (1 mole) of theophylline and 219.20 g (1.5 moles) of lysine are hot-dissolved in 400 ml of H_2O . The solution is concentrated under vacuum until dryness, the bath temperature being kept lower than
- 70 50°C.

The residue is crystallised from 4.5 l of 96% ethyl alcohol. The precipitate, obtained by cooling the solution under stirring, is filtered.

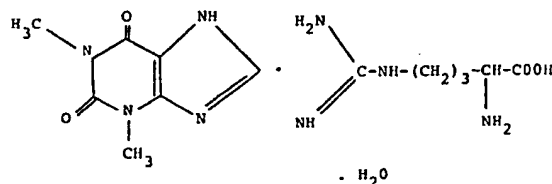
75 260 g: Yield 80% mp: 195-205°C (decomposition)

Example II

Arginine Theophyllinate.

Empirical formula : $C_{13}H_{22}N_8O_4 \cdot H_2O$

80 Structural formula:



Molecular weight : 372/38

N Contents : 30.09%

Composition : Theophylline 48.38%, Arginine 46.78% H_2O 4.84%.

85 Preparation process.

- 180.17 g (1 mole) of theophylline and 174.20 g (1 mole) of arginine are hot-dissolved in 800 ml of H_2O . The cooling of the solution forms a crystalline precipitate (320 g) having a melting point of 200-205°C (decomposition). Yield 86%.

The identity and purity of the salts can be determined by the following analytical operations:

- (a) nitrogen test according to the Dumas method
(b) titration of amine nitrogen by the potentiometric method in anhydrous environment (solvent: glacial acetic acid) by means of $HClO_4$ 0.1N in glacial acetic acid.

(c) UV spectrophotometric titration in HCl 0.1N. The pharmaceutical activity has been preliminarily

100 checked by the determination of:

LD_{50} per os in the mouse

Lysine theophyllinate 1.12 m Mole/kg

Arginine theophyllinate 1.75 m Mole/kg

- Antibronchospastic activity in awake guinea-pigs according to the modified Armitage's method (Brit. J. Pharmacol. 16, 59; 1961); the activity is expressed as an index with respect to the theophylline made equal to 1.

Lysine theophyllinate 1.08

110 Arginine theophyllinate 0.8

Some data relevant to tests made in animals and in men by using the pharmaceutical compositions of the invention are reported herebelow.

The lysine theophyllinate has been administered *per os* during 3 months to male and female Wistar rats at the doses of 36-145 mg/Kg/pro die.

The comparison with control animals has given evidence of its good tolerance.

Subsequently the pharmaceutical composition has been tested in clinical practice in 3 groups of patients of paediatric age between 8 months and 13 years, suffering from asthmatic affections. These are determined:

- Respiratory functionality
- Hematologic and hematochemical values
- Hematic rates and, only in a group, the concentration of theophylline in the saliva
- Cardiocirculatory effects
- Tolerance.

In all the tests, the composition according to the invention has been administered in the form of drops and tablets every 6-8 hours at a dose of 4-6 mg/kg depending on the patient's age.

The pharmaceutical composition of the invention has always dominated the symptomatology and obtained a significant improvement of the hemogasmetring and ventilation parameters.

The best absorption of the active constituent in the administration is in the form of drops and tablets, which may be otherwise deducted from the study of the hematic levels of theophylline.

There is additionally an excellent gastroenteric tolerance and an absence of clinical significant alterations with respect to the biohumoral parameters under consideration.

The salts which form the object of the present invention can be utilised in pharmaceutical preparations as capsules, tablets, sugar-coated pills, retarded release tablets and capsules, drops, syrups, phials, and suppositories suited to administration in human therapy.

The following Examples illustrate some preferred preparations obtained by utilising the products of the invention.

Example III.

Lysine theophyllinate
Divisible tablets for paediatric therapy.

Each divisible tablet contains:

Lysine theophyllinate	mg 182
(corresponding to 100 mg of anhydrous theophyllinate)	
Starch	mg 36
Carboxymethylcellulose	mg 8
Talc	mg 10
Magnesium stearate	mg 5.

Drops for pediatric use.

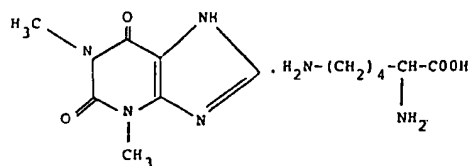
Each bottle containing lyophilized lysine theophyllinate has the following composition:

Lysine theophyllinate	mg 725
(corresponding to 400 mg of anhydrous theophylline)	
Mannite	mg 800
Each solvent bottle contains:	
Alcohol (96%)	ml 2
Purified water q. s. to 10 ml.	

CLAIMS:

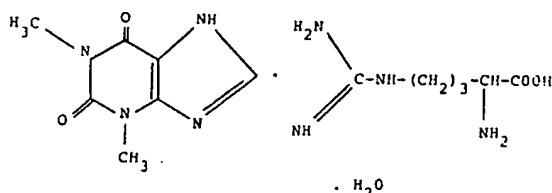
1. An antibronchospastic pharmaceutical, water-soluble composition comprising a theophylline salt with a basic amino acid.

2. An antibronchospastic pharmaceutical composition as claimed in claim 1 and of formula:



in which the basic amino acid is lysine.

3. An antibronchospastic pharmaceutical composition as claimed in claim 1 and of formula:



in which the basic amino acid is arginine.

4. Antibronchospastic pharmaceutical preparations comprising a theophyllinic water-soluble composition as claimed in claim 1.

5. Antibronchospastic pharmaceutical preparations comprising a theophylline salt with lysine as claimed in claim 2.

6. An antibronchospastic pharmaceutical preparation comprising a theophylline salt with arginine as claimed in claim 3.

7. An antibronchospastic pharmaceutical preparation as claimed in any one of claims 4 to 6, and suited to the parenteral, oral, or rectal administration.

8. Lyophilised antibronchospastic pharmaceutical preparations as claimed in any one of claims 4 to 6, and suited to the oral and parenteral administration.

9. A process of preparing a composition as claimed in claim 2, comprising the steps of concentrating to dryness an aqueous solution of theophylline and lysine in a molar ratio of 1 : 1.5 and crystallising the residue from 96% ethanol.

10. A process of preparing the composition as claimed in claim 3, comprising the step of precipitating arginine theophyllinate from a hot saturated, aqueous solution of theophylline and arginine in a molar ratio of 1 : 1.

11. An antibronchospastic, pharmaceutical water-soluble composition comprising a theophylline salt with a basic amino acid substantially as described hereinabove and with reference to the Examples.

12. A process of preparing an antibronchospastic, pharmaceutical water-soluble composition comprising a theophylline salt with a basic amino acid substantially as described hereinabove and with reference to the Examples.